



**DECLARATION UNDER 37  
C.F.R. § 1.132 OF DR.  
JOSEPH M. PATTI, PH.D.**

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Commissioner for Patents  
P.O. Box 1450

I, Dr. Joseph Patti, Ph.D., declare and state as follows:

1. I am currently the Vice President of Research and Development for Inhibitex, a company that specializes in research and products regarding extracellular matrix proteins and monoclonal antibodies generated thereto including those embodied in the present invention. I have also been involved in the preparation and clinical testing of products developed in accordance with some of the proteins and antibodies of the present application. In addition to being a co-inventor of numerous US Patents in this general field, including U.S. Pat. No. 6,288,214 for Collagen Binding Protein Compositions and Methods of Use, U.S. Pat. No. 6,680,195, for Extracellular matrix-binding proteins from *Staphylococcus aureus*, U.S. Pat. No. 6,685,943, Fibronectin binding protein compositions and methods of use, and U.S. Pat. No. 6,692,739, Staphylococcal immunotherapeutics via donor selection and donor stimulation, and I have also authored or co-authored numerous journal articles in this field. I am thus well familiar with the subject matter of the present invention.

2. The present invention was developed in an effort to provide additional means for treating and preventing staphylococcal infection through focusing on extracellular matrix binding proteins which enable bacteria to attack, invade and infect host

organisms. In this regard, a team at Inhibitex investigated several binding proteins from *Staphylococcus aureus* and *Staphylococcus epidermidis*, and ultimately arrived at a composition wherein purified donor plasma was obtained which contained high titers of antibodies to the clumping factor A (ClfA) protein from *S. aureus* and the serine-aspartate dipeptide repeat protein G (SdrG) from *S. epidermidis*. This purified donor plasma is obtained by screening plasma using the SdrG A domain which is the protein region located at amino acids 51-598 of the SdrG protein which is SEQ ID NO: 10 of the present application. This purified donor plasma product obtained in this manner was identified as "Veronate®" and was tested in pre-clinical and clinical trials.

3. As indicated in Exhibit 1 attached herewith, a copy of which has been previously made of record in this application, Veronate® had been subject to preclinical in vivo tests, and clinical trials, and the results of these tests are highlighted in Exhibit 1 which was prepared under my supervision. Although later clinical trials did not obtain results at the same levels, the testing reflected in Exhibit 1 indicated that Veronate® was able to reduce or prevent incidence of infection from *S. epidermidis*. The differing results are most likely due to the immaturity of the very low birth weight infant's polymorphonuclear cells.

4. To confirm that the SdrG component in Veronate® was crucial in the protective effect, additional tests were conducted on Veronate® which reflected the biological role that the anti-SdrG component played in the protection against *S. epidermidis* infection. These results are attached hereto as Exhibit 2. In these tests, a

Veronate® product depleted of SdrG specific antibodies was tested in vivo and compared to Veronate® that contained the anti-SdrG antibodies. As shown in Exhibit 2, the data showed clearly that the normal Veronate® product which contained SdrG antibodies was able to protect against challenge from *S. epidermidis* in vivo. On the other hand, the specific removal of SdrG specific antibodies from Veronate® produced an antibody preparation that was not protective in a rabbit model of infectious endocarditis.

5. Similarly, this work was repeated with regard to the protein Fbe, a protein which is structurally very similar to SdrG and which some in the scientific community consider another name for SdrG. In this case, as reflected in an article by Rennermalm et al., attached hereto as Exhibit 3, a series of in vivo tests were conducted with regard to antibodies to Fbe, and Fbe antibodies were given intravenously to mice.(see page 3082, right column, last paragraph). The mice were then tested for severity of infection and bacterial load. As shown in Exhibit 3, the bacterial proliferation was greatly reduced in vivo in the mice treated with anti-Fbe antibodies, and this showed a protective effect of the anti-Fbe antibodies. See page 3083, left side. In addition, the authors of the article noticed a correlation between opsonization and fibrinogen binding capacity, which reflected that the antibodies were able to disrupt the fibrinogen binding ability of *S. epidermidis*.

6. The Rennermalm article attached It is thus clear that one skilled in the art would be able to make and use the present invention, namely treating or preventing an *S. epidermidis* infection using antibodies capable of binding to the A domain of the SdrG protein of *S. epidermidis*. In particular, the in vivo test results from Inhibitex and from

the Rennermalm group were obtained using polyclonal antibodies that were obtained using conventional techniques well available to those of ordinary skill in the art.

7. Indeed, in light of the fact that polyclonal antibodies generally have multiple epitopes, it was not necessary to determine where the epitopes were in order to carry out the method of the invention, namely using those antibodies in methods of protecting against *S. epidermidis* infection. Accordingly, by identifying the A domain to SdrG and preparing antibodies thereto that could disrupt fibrinogen binding and could be used as passive vaccines against infection or for preventing adherence of *S. epidermidis* to host cells or prosthetic devices, the invention as presently claimed was clearly described in the specification and the claimed steps were in the possession of the inventors at the time of the filing of the present application. Moreover, as reflected in our results and in the results of the Rennermalm article, these methods can be carried out using routine experimentation well within the scope of the ones regularly employed by those skilled in this art. One of ordinary skill in the art would thus readily be able to practice the present invention, namely inhibiting fibrinogen binding and treating or preventing *S. epidermidis* infection using the antibodies to the SdrG A domain.

I hereby state that all statements made herein based on my own personal knowledge are true and correct and that all statements based on my information and belief are true and correct to the best of my knowledge, and further that all of these statements have been made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2/9/07  
Date

Joseph M. Patti  
Dr. Joseph M. Patti, Ph.D.

# ***Update on Veronate***

Seth Hetherington, M.D.  
Chief Medical Officer, VP Clinical Development  
Inhibitex, Inc.

EXHIBIT 1



# Veronate®

- Plasma-derived, donor-selected polyclonal IVIG
- High levels of IgG directed against staphylococcal proteins (MSCRAMM®)
  - *S. aureus* - ClfA
  - *S. epidermidis* - SdrG
- Formulated for premature infants
  - 0.2% NaCl
  - No sucrose
  - No preservative



# **Veronate® – Target Indication**

- Premature infants, 500 to 1250 grams
- Prevention of nosocomial infections due to:
  - *S. aureus*
  - *S. epidermidis*
- Other potential benefits
  - Reduction in candidemia
  - Reduce overall mortality

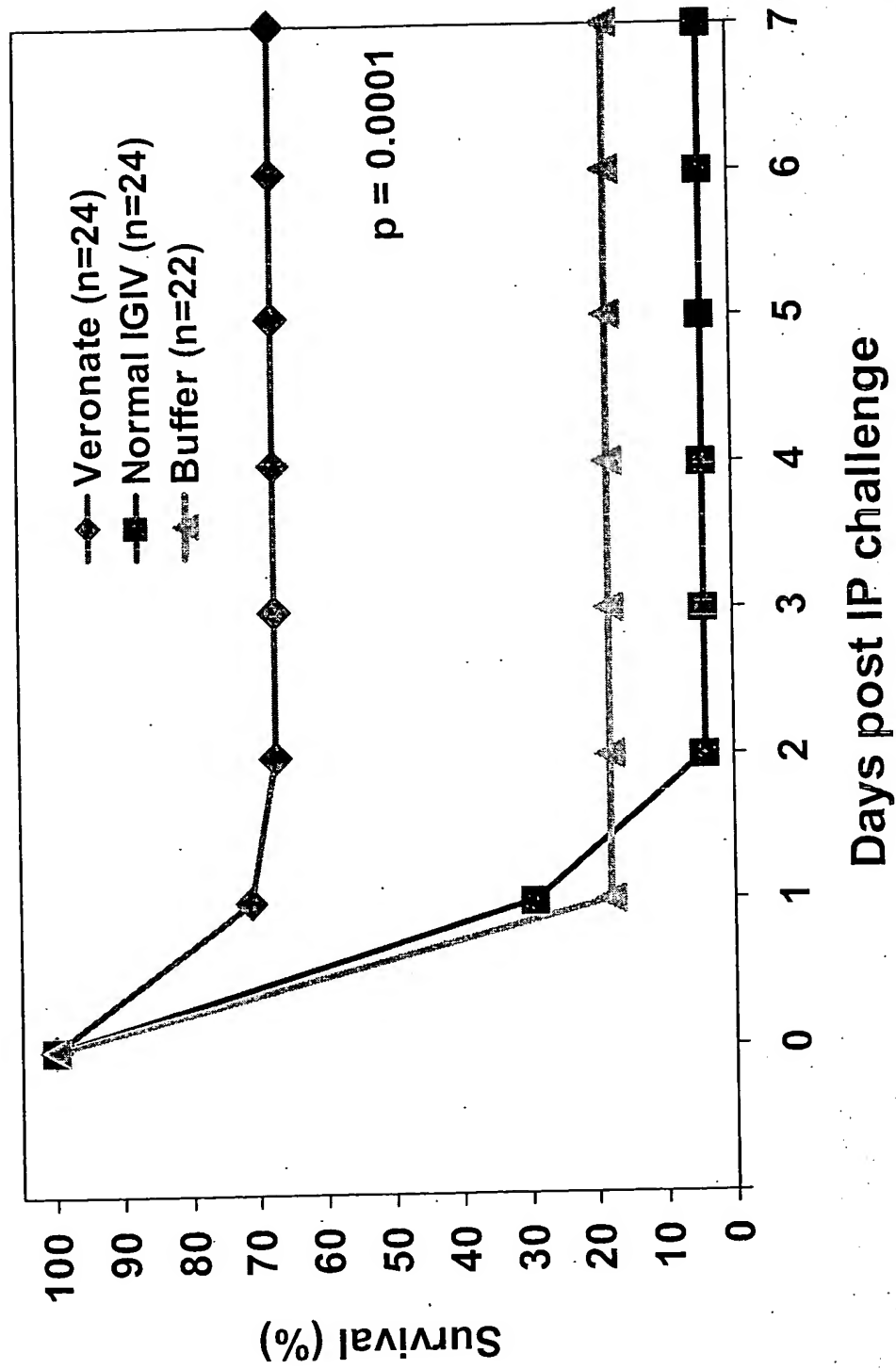




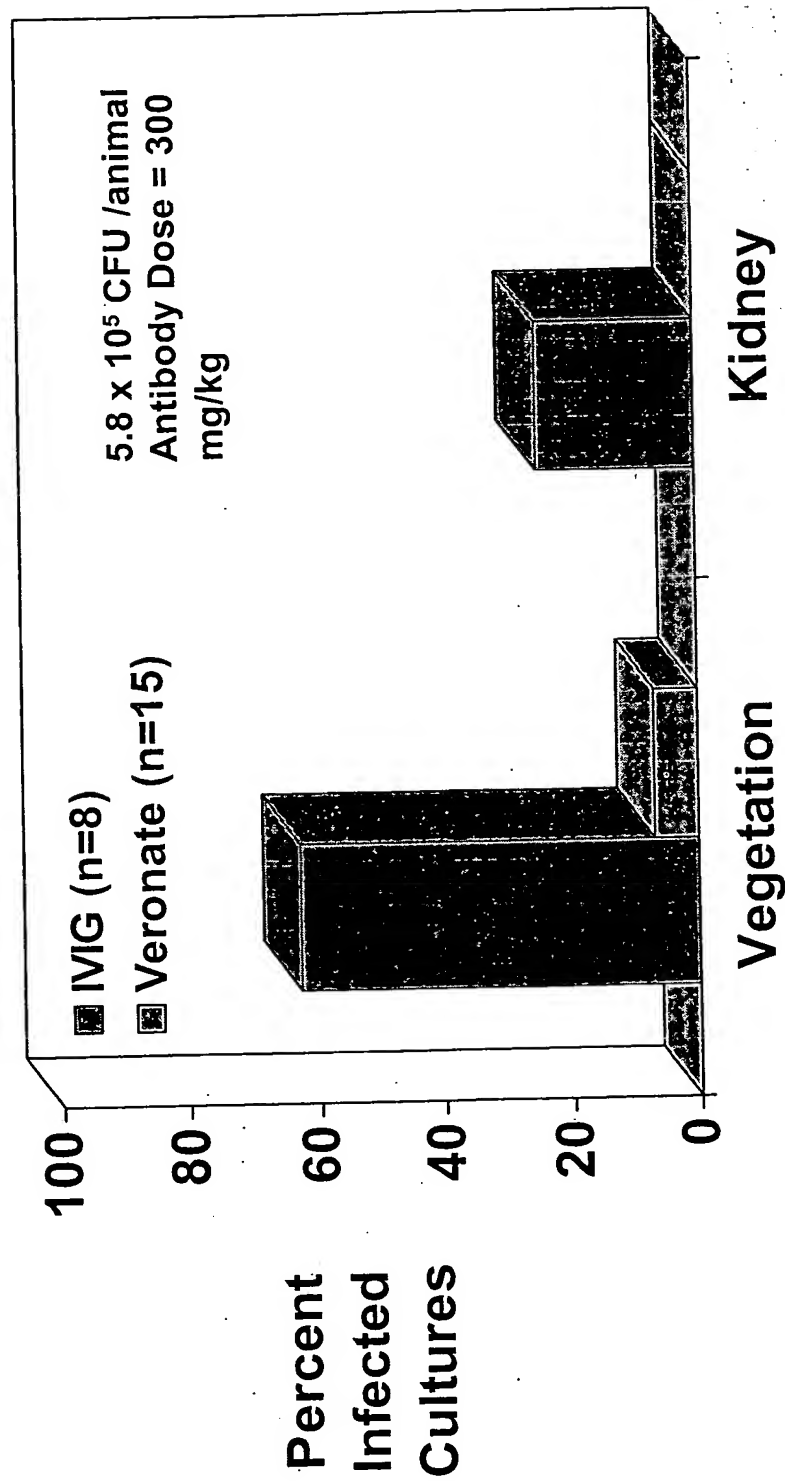
# ***Pre-Clinical Studies***

- Reduced mortality from *S. epidermidis* infection in 3-6 day old rats
- Reduced *S. aureus* and *S. epidermidis* bacteremia and tissue invasion in ***prophylaxis*** rabbit endocarditis model
- Reduced tissue invasion by both *S. aureus* and *S. epidermidis* in ***treatment*** of endocarditis in rabbit model

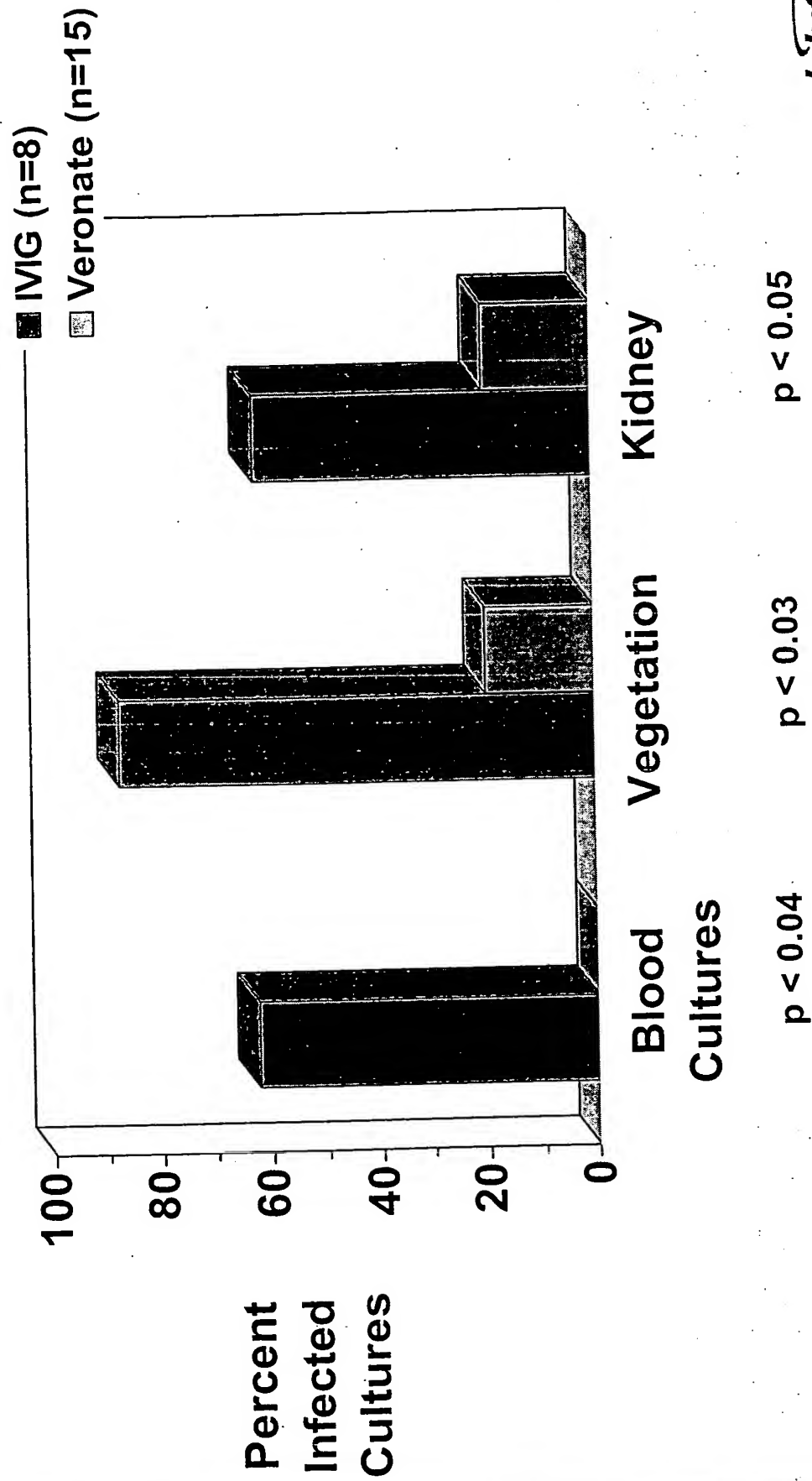
# Veronate Prevents *S. epidermidis* Mediated Mortality in a Suckling Rat Model



# Veronate Reduces the Incidence of *S. aureus* Infection in a Rabbit Model of Infectious Endocarditis



# Veronate Reduces the Incidence of *S. epidermidis* Infection in a Rabbit Model of Infectious Endocarditis



# Summary of Phase II Results

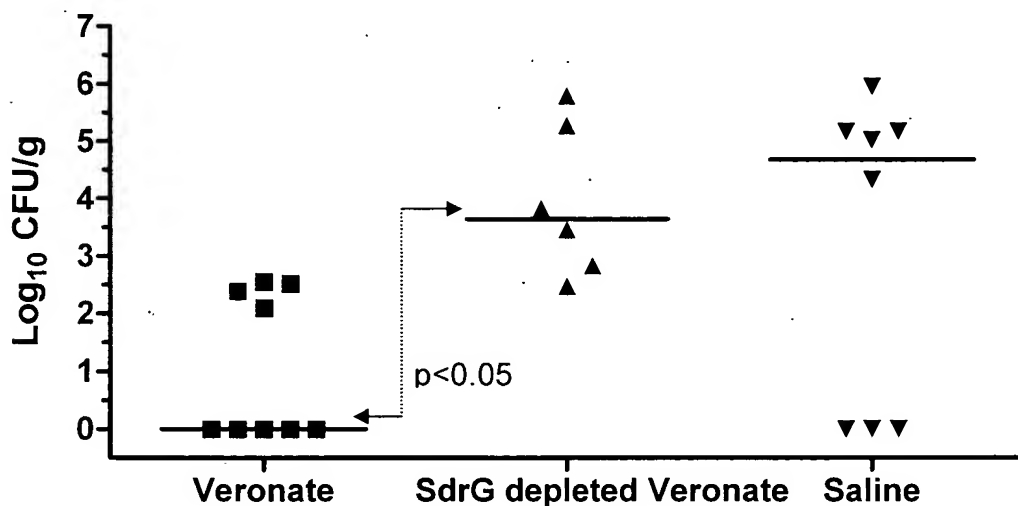
- Veronate was well tolerated
  - 1,280 doses administered
- No significant difference in AE's or SAE's between placebo and treatment groups
- 750 mg/kg dose selected for pivotal Phase III trial
- Relative reductions between placebo and 750 mg/kg treatment cohorts on an intent-to-treat basis:
  - *S. aureus* infections – 63%
  - Fungal infections – 67%
  - All-cause mortality – 36%

# ***Summary of the Trends in Phase II***

- Magnitude of the observed differences in infection rates ~60%
- Differences observed at the highest dose tested
- Dose-response by time-to-onset analysis
- Differences for the Veronate targeted organisms
- Lack of effect on non-targeted organisms
  - Biologically plausible link to *Candida* spp

## EXHIBIT 2

Veronate<sup>®</sup> was prepared with plasma collected from donors with elevated antibody levels recognizing the MSCRAMM<sup>®</sup> proteins clumping factor A (ClfA) from *S. aureus* and serine-aspartate dipeptide repeat G (SdrG) from *S. epidermidis*. To investigate the biological role that anti-SdrG antibodies play in the protection against *S. epidermidis* infection, catheterized rabbits were administered 300 mg/kg Veronate, 300 mg/kg of Veronate depleted in SdrG specific antibodies or saline intravenously. The rabbits were challenged 20 hours later with  $3.5 \times 10^6$  CFU *S. epidermidis* ATCC 35984. Tissue samples from the kidneys were harvested and cultured. Symbols indicate results from individual animals. Ratios listed on the x-axis indicate the incidence of infection. Horizontal lines indicate group medians. Significant *P* values are indicated on the graph.



**Figure 1. Comparison of Veronate and SdrG depleted Veronate in the rabbit model of *S. epidermidis* mediated infective endocarditis.**

These data clearly indicate that Veronate, which contains elevated levels of SdrG antibodies, protects against *S. epidermidis* IV challenge. In contrast, the specific removal of SdrG specific antibodies from Veronate produces an antibody preparation that is not protective in a rabbit model of infectious endocarditis.

## The Fibrinogen Binding Protein of *Staphylococcus epidermidis* Is a Target for Opsonic Antibodies

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Antibodies against the fibrinogen binding protein (Fbe) of *Staphylococcus epidermidis* significantly increased macrophage phagocytosis. Antibodies against autolysin E were opsonic but to a lesser extent. Antibodies against a novel, putatively surface-located antigen were unable to enhance phagocytosis. The severity of systemic infection of mice with *S. epidermidis* was reduced if the bacteria were preopsonized with anti-Fbe prior to administration. Fbe is thus a strong candidate for protein vaccination against *S. epidermidis* infection, and antibodies against Fbe can be used to prevent or treat infections caused by *S. epidermidis*.

*Staphylococcus epidermidis* is a major nosocomial pathogen. It is a common etiologic agent in neonatal septicemia and in peritonitis, causing mainly foreign body-associated infections. In patients, proteins such as albumin, fibrinogen, fibronectin, and von Willebrand factor rapidly cover implants (3). *S. epidermidis* possesses an unknown number of proteins that contribute to specific adhesion to these molecules. Several studies also demonstrate the important roles of biofilm formation and the polysaccharide intracellular adhesin/hemagglutinin in pathogenicity (17, 18).

Fbe is a 119-kDa fibrinogen binding protein located at the surface of *S. epidermidis* and is present in most tested strains of *S. epidermidis* (11). Fbe has also been named SdrG (1). It is structurally related to other staphylococcal surface-located proteins, such as ClfA of *S. aureus* (9, 15). *S. epidermidis* interaction with peripheral venous catheters from patients, which spontaneously become coated with fibrinogen (5), is blocked by anti-Fbe antibodies (13). Fbe is expressed on the surface of *S. epidermidis* during infection, as indicated by an increase of anti-Fbe titers in sera from patients infected with *S. epidermidis* (8).

Macrophages are of vital importance in suppressing *S. epidermidis* infections (10). Phagocytic activity of macrophages is greatly enhanced if specific antibodies are attached to the pathogen (12).

In this study, we demonstrate that fresh alveolar macrophages from rat ingest and kill *S. epidermidis* opsonized with anti-Fbe antibodies to a much higher extent than they ingest and kill nonopsonized bacteria or bacteria opsonized with antibodies directed against AtlE (4) or another putative surface antigen, Embp (19).

In the first experiment, *S. epidermidis* (strain 19) was opsonized with antibodies and added to macrophages. The bacteria, grown in broth for 2 h (optimal for expression of fibrinogen binding), were washed, adjusted to a concentration of 10<sup>8</sup>

CFU/ml, mixed with antibodies (300-μg/ml final concentration), and incubated at 37°C for 1 h. The antibodies used for opsonization were rat or rabbit antibodies against three antigens: glutathione-S-transferase fused to Fbe (GST-Fbe), Embp, and AtlE. As controls, phosphate-buffered saline or antibodies taken before immunization were used. GST-Fbe was produced as previously described (15). Embp is a fibronectin binding protein (19). The fibronectin binding domain of Embp, a 207-amino-acid region, was amplified by PCR using DNA from *S. epidermidis* strain 19 with primers 5'-AATTAACCATGGCTGATAAGAAATTTACAAATTGAAT (forward) and 5'-AATTAACCCGGGTATTGCAGCTTTTTGAGCATT (reverse); extending NcoI and SmaI sites, respectively, are underlined. Pwo DNA polymerase was used. Running cycles were as follows: 2 min at 96°C followed by 30 cycles of 15 s at 96°C, 30 s at 50°C, and 2 min (prolonged by an additional 20 s for each cycle after the 11th cycle) at 72°C. Cleavage of the PCR product with NcoI and SmaI permitted directional in-frame cloning into the expression vector pTYB4 belonging to the IMPACT T7 system (New England Biolabs). The ligated DNA was used to electrotransform *Escherichia coli* strain ER2566. A plasmid harboring the insert was isolated from a transformant and verified by DNA sequencing. The resulting protein is hereafter termed Embp, although it contains only the fibronectin binding portion. Expression and purification of Embp was performed as described in the protocol provided from the manufacturer of the IMPACT T7 system.

Autolysin E, AtlE, is a 60-kDa surface-located homologue of *S. aureus* major autolysin. It mediates adherence to polystyrene materials and binds specifically to vitronectin (4, 7). An *S. epidermidis* mutant lacking AtlE is less infectious in a rat central venous catheter infection model, indicating a role for AtlE in pathogenesis (16). AtlE was a kind gift from Friedrich Götz, Mikrobielle Genetik, Universität Tübingen, Tübingen, Germany.

Antibodies against these antigens were raised in rabbit, rat, or sheep. Subcutaneous immunizations were done at 2-week intervals by using 20 μg of protein. Freund's complete adjuvant was used at the first immunization, which was followed by two booster doses of Freund's incomplete adjuvant. One rat was mock immunized with Freund's adjuvant alone. Antibodies were purified from immune and preimmune sera by separation

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TABLE 1. Phagocytosis of *S. epidermidis* strain 19 opsonized with different antibodies<sup>a</sup>

Origin of antibody	Antibody	Mean log <sub>10</sub> no. of CFU ingested	SD in log <sub>10</sub> no. of CFU ingested
Rat	Fbe	5.5	4.9
	Embp	3.3	2.4
	Normal IgG	3.2	3.0
Rabbit	Fbe	5.7	5.3
	AtIE	4.8	4.6
	Normal IgG	3.8	3.7
Sheep	Fbe	5.6	5.5
	Normal IgG	3.8	3.7

<sup>a</sup> Log<sub>10</sub> numbers of CFU of ingested bacteria are shown. *S. epidermidis* strain 19 (10<sup>7</sup> CFU), cultured for 2 h, was opsonized with purified antibodies (300 µg/ml) against Fbe, Embp, AtIE, or normal IgG. The antibodies originated from rat, rabbit, or sheep. Significantly (*t* test) more bacteria opsonized with anti-Fbe antibodies were ingested by alveolar macrophages isolated by rat BAL than bacteria opsonized with anti-AtIE (*P* < 0.001), anti-Embp (*P* < 0.001), or normal IgG (*P* < 0.001). Bacteria opsonized with anti-AtIE were ingested to a higher extent than bacteria opsonized with normal IgG (*P* < 0.05). Standard deviations are shown (*n* = 4 for all tests).

on protein G Sepharose 4 fast flow (Pharmacia Amersham). Therefore, all phagocytosis experiments were performed without complement present. The antibody concentration was set to ca. 3 mg/ml. Total and specific immunoglobulin G (IgG) titers were determined for each antibody or serum preparation by conventional enzyme-linked immunosorbent assay (data not shown). The coating concentrations were 1 µg/well for GST-Fbe and AtIE and 0.1 µg/well for Embp. No cross-reactivity among the proteins was found.

Rabbit sera against GST-Fbe or AtIE were gifts from Åsa Ljungh, Lund University. Sheep sera against GST-Fbe were gifts from Per Månsson, SBL Vaccine, Stockholm, Sweden.

For macrophage ingestion studies, 10<sup>7</sup> opsonized bacteria in culture media were added to the macrophages attached to 24-well plates. Macrophages were obtained from rats (average weight, 180 g; Wistar) by bronchoalveolar lavage as described elsewhere (2, 6). The macrophages were adjusted to a concentration of 10<sup>6</sup> cells/ml and added to a 24-well cell culture plate (Nunc) at 10<sup>6</sup> cells/well. The plates were stored at 4°C for 1 h for adherence, and then red blood cells and other nonadherent cells were washed away with Hanks balanced salt solution (Gibco). The plates with infected macrophages were incubated with 7% CO<sub>2</sub> at 37°C. The optimal incubation time was found to be 2 h. Extracellular bacteria were gently washed away, and the remaining bacteria were killed by treatment with lyso-staphin at 50 µg/ml for 30 min. The plates were centrifuged at 110 × g, and the supernatants were discarded. The cells were lysed and detached with 1 M NaCl. Microscopic examination revealed lysis of all eukaryotic cells. The bottoms of the wells were scraped, and the contents were serially diluted and plated onto blood agar plates.

As shown in Table 1, the number of bacteria ingested into macrophages varied considerably depending on the opsonizing antibody used. Maximum ingestion was equivalent to 10 bacteria/macrophage, corresponding to half the number of the inoculated bacteria. With no antibodies added, less than 0.01 CFU/cell was found after 2 h of incubation.

Of the antibodies tested, only antibodies against Fbe and AtIE were effective as opsonizers. *S. epidermidis* strain 19 was

ingested 177 times better when opsonized with rat anti-Fbe antibodies than when opsonized with the rat preimmune antibody controls (*P* < 0.001) and 144 times better than when opsonized with rat antibodies against Embp (*P* < 0.001). Antibodies directed against Embp were no better opsonizers than phosphate-buffered saline (data not shown) or preimmune antibodies (*P* > 0.05). Rabbit anti-AtIE antibodies enhanced phagocytosis by 11 times (*P* < 0.05) compared with normal rabbit IgG controls. However, rabbit anti-Fbe antibodies were eight times more effective in opsonization than rabbit anti-AtIE (*P* < 0.001) and 80 times more effective than normal IgG (*P* < 0.001). Sheep antibodies directed against Fbe enhanced phagocytosis by 60 times (*P* < 0.001) compared with preimmune IgG from the same animal (Table 1).

Quantification was also done by using serial dilutions of rabbit antibodies. An approximately 20-fold-higher concentration of anti-AtIE antibodies was required to reach the same level of phagocytosis of *S. epidermidis* strain 19 as that reached with anti-Fbe antibodies (data not shown).

To study the rate of killing of ingested bacteria, macrophages which had ingested bacteria for 2 h were kept for an additional 0, 2, and 16 h after treatment with lyso-staphin. Intra- and extracellular bacteria were then enumerated. The bacteria could persist intracellularly for more than 2 h after termination of phagocytosis and even seemed to increase in numbers. However, after 18 h of incubation there was substantial killing; only about 1% of the ingested bacteria remained after this time (data not shown).

The bacterial strain variation was assessed by using seven different strains of *S. epidermidis* and one *S. aureus* strain in opsonization experiments with anti-Fbe antibodies. All the strains possess the *fbe* gene, except STO 56 (*fbe::eryR* mutant isogenic with strain HB) (14) and *S. aureus* strain Newman. All strains tested were better phagocytosed after opsonization with anti-Fbe antibodies than after opsonization with preimmune antibodies. The enhancement factors were 108 (for strain 19), 93, 45, 15, 1.5, and 1.2 (*P* < 0.05 for all strains). The strains lacking Fbe, *S. epidermidis* STO 56 and *S. aureus* Newman, were not stimulated at all with anti-Fbe antibodies (data not shown).

All these strains were also tested for their capacity to bind to fibrinogen by using a method described earlier (11). Although all strains have the *fbe* gene, binding to fibrinogen varied considerably (data not shown), presumably due to various levels of expression of Fbe or various levels of exposure on the surface.

A correlation between the fibrinogen binding capacity of these strains and opsonization with anti-Fbe antibodies was clearly seen. The correlation between the two parameters is linear with a correlation coefficient *r* of 0.83 (*P* < 0.05) as determined using the least-square method. Thus, opsonization with antibodies against Fbe increases phagocytosis and killing of *S. epidermidis* strains relative to their fibrinogen binding capacities.

To evaluate the protective effect of anti-Fbe antibodies in vivo, opsonized bacteria were given intravenously to mice. *S. epidermidis* strain 19 was concentrated to 10<sup>9</sup> CFU/ml and incubated with 10% serum for 1 h at 37°C, and 100 µl was given intravenously to ~30-g female Naval Medical Research Institute (NMRI) mice (25 mice/group). The serum used was sheep anti-GST-Fbe (obtained from Per Månsson, SBL Vac-

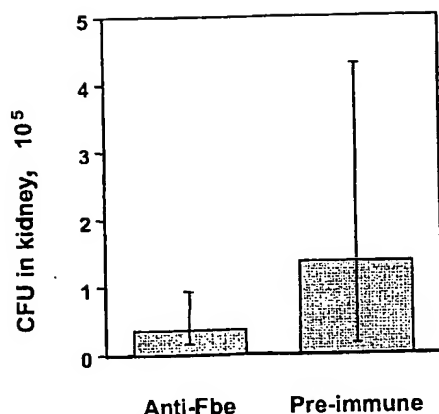


FIG. 1. Bacterial loads in mouse kidneys after infection with preopsonized *S. epidermidis* strain 19. Mice were infected with bacteria preopsonized with serum against Fbe or normal serum. Bacterial loads in kidneys after 4 days were significantly lower ( $P < 0.05$ ; median test) in mice inoculated with bacteria preopsonized with anti-Fbe (median,  $3.2 \times 10^4$  CFU; upper quartile,  $9.1 \times 10^4$  CFU; lower quartile,  $8.2 \times 10^3$  CFU) than in those inoculated with bacteria preopsonized with normal serum (median,  $1.3 \times 10^5$  CFU; upper quartile,  $4.3 \times 10^5$  CFU; lower quartile,  $5.9 \times 10^3$  CFU).

cine) or normal sheep serum as a control. The severity of bacterial infection was determined by measuring the bacterial numbers in the kidneys after 4 days. The bacterial load in the kidneys is an indication of the total bacterial load in the body. As shown in Fig. 1, preopsonization of bacteria with anti-Fbe serum led to a lower level of bacterial proliferation (median,  $3.2 \times 10^4$  CFU; upper quartile,  $9.1 \times 10^4$  CFU; lower quartile,  $8.2 \times 10^3$  CFU) than preopsonization of bacteria with normal serum (median,  $1.3 \times 10^5$  CFU; upper quartile,  $4.3 \times 10^5$  CFU; lower quartile,  $5.9 \times 10^3$  CFU) ( $P < 0.05$ ), thus indicating a protective effect of these antibodies.

Taken together, these findings show that antibodies against Fbe have the capacity to opsonize and increase phagocytosis of *S. epidermidis* in vitro and to decrease the severity of experimental infection in mice. Fbe is thus a strong candidate for continued development of antibody-mediated therapy or prophylaxis against infection.

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We thank Ingegerd Löfving Arvholm for excellent technical assistance.

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## REFERENCES

- Davis, S., S. Gurusiddappa, K. W. McCrea, S. Perkins, and M. Höök. 2001. SdrG, a fibrinogen-binding bacterial adhesin of the microbial surface components recognizing adhesive matrix molecules subfamily from *Staphylococcus epidermidis*, targets the thrombin cleavage site in the B $\beta$  chain. *J. Biol. Chem.* 276:27799–27805.
- Dethloff, L. A., B. C. Gladen, L. B. Gilmore, and G. E. Hook. 1987. Quantitation of cellular and extracellular constituents of the pulmonary lining in rats by using bronchoalveolar lavage. Effects of silica-induced pulmonary inflammation. *Am. Rev. Respir. Dis.* 136:899–907.
- Francois, P., J. Schrenzel, C. Stoerman-Chopard, H. Favre, M. Herrmann, T. J. Foster, D. P. Lew, and P. Vaudaux. 2000. Identification of plasma proteins adsorbed on hemodialysis tubing that promote *Staphylococcus aureus* adhesion. *J. Lab. Clin. Med.* 135:32–42.
- Heilmann, C., M. Hussain, G. Peters, and F. Gotz. 1997. Evidence for autolysin-mediated primary attachment of *Staphylococcus epidermidis* to a polystyrene surface. *Mol. Microbiol.* 24:1013–1024.
- Herrmann, M., P. E. Vaudaux, D. Pittet, R. Auckenthaler, P. D. Lew, F. Schumacher-Perdreau, G. Peters, and F. A. Waldvogel. 1988. Fibronectin, fibrinogen, and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. *J. Infect. Dis.* 158:693–701.
- Lavnikova, N., S. Prokhorova, L. Helyar, and D. L. Laskin. 1993. Isolation and partial characterization of subpopulations of alveolar macrophages, granulocytes, and highly enriched interstitial macrophages from rat lung. *Am. J. Respir. Cell Mol. Biol.* 8:384–392.
- Li, D. Q., F. Lundberg, and A. Ljungh. 2001. Characterization of vitronectin-binding proteins of *Staphylococcus epidermidis*. *Curr. Microbiol.* 42:361–367.
- McCrea, K. W., O. Hartford, S. Davis, D. N. Eidhin, G. Lina, P. Speziale, T. J. Foster, and M. Hook. 2000. The serine-aspartate repeat (Sdr) protein family in *Staphylococcus epidermidis*. *Microbiology* 146:1535–1546.
- McDevitt, D., P. Francois, P. Vaudaux, and T. J. Foster. 1994. Molecular characterization of the clumping factor (fibrinogen receptor) of *Staphylococcus aureus*. *Mol. Microbiol.* 11:237–248.
- Meddens, M. J., J. Thompson, W. C. Bauer, J. Hermans, and R. van Furth. 1983. Role of granulocytes and monocytes in experimental *Staphylococcus epidermidis* endocarditis. *Infect. Immun.* 41:145–153.
- Nilsson, M., L. Frykberg, J.-I. Flock, L. Pei, M. Lindberg, and B. Guss. 1998. A fibrinogen-binding protein of *Staphylococcus epidermidis*. *Infect. Immun.* 66:2666–2673.
- Ohman, L., G. Maluszynska, K. E. Magnusson, and O. Stendahl. 1988. Surface interaction between bacteria and phagocytic cells. *Prog. Drug Res.* 32:131–147.
- Pei, L., and J.-I. Flock. 2001. Functional study of antibodies against a fibrinogen-binding protein in *Staphylococcus epidermidis* adherence to polyethylene catheters. *J. Infect. Dis.* 184:52–55.
- Pei, L., and J.-I. Flock. 2001. Lack of fbe, the gene for a fibrinogen-binding protein from *Staphylococcus epidermidis*, reduces its adherence to fibrinogen coated surfaces. *Microb. Pathog.* 31:185–193.
- Pei, L., M. Palma, M. Nilsson, B. Guss, and J.-I. Flock. 1999. Functional studies of a fibrinogen binding protein from *Staphylococcus epidermidis*. *Infect. Immun.* 67:4525–4530.
- Rupp, M. E., P. D. Fey, C. Heilmann, and F. Gotz. 2001. Characterization of the importance of *Staphylococcus epidermidis* autolysin and polysaccharide intercellular adhesin in the pathogenesis of intravascular catheter-associated infection in a rat model. *J. Infect. Dis.* 183:1038–1042.
- Rupp, M. E., J. S. Ulphani, P. D. Fey, and D. Mack. 1999. Characterization of *Staphylococcus epidermidis* polysaccharide intercellular adhesin/hemagglutinin in the pathogenesis of intravascular catheter-associated infection in a rat model. *Infect. Immun.* 67:2656–2659.
- Shiro, H., G. Meluleni, A. Groll, E. Muller, T. D. Tosteson, D. A. Goldmann, and G. B. Pier. 1995. The pathogenic role of *Staphylococcus epidermidis* capsular polysaccharide/adhesin in a low-inoculum rabbit model of prosthetic valve endocarditis. *Circulation* 92:2715–2722.
- Williams, R. J., B. Henderson, L. J. Sharp, and S. P. Nair. 2002. Identification of a fibronectin-binding protein from *Staphylococcus epidermidis*. *Infect. Immun.* 70:6805–6810.